Clinical Immunology – Review Article

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2019;179:231–245
DOI: 10.1159/000499044

Received: January 4, 2019
Accepted after revision: February 18, 2019
Published online: May 15, 2019

The Heterogeneous Pathogenesis of Selective Immunoglobulin A Deficiency

Yasser Bagheri[a–c] Roozbeh Sanaei[d, e] Reza Yazdani[b] Mehdi Shekarabi[c, d] Reza Falak[c, d] Javad Mohammadi[f] Hassan Abolhassani[b, g] Asghar Aghamohammadi[b]

[a]Clinical Research Development Unit (CRDU), 5 Azar Hospital, Golestan University of Medical Sciences, Gorgan, Iran; [b]Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran; [c]Department of Immunology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; [d]Immunology Research Center (IRC), Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran; [e]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran; [f]Department of Biomedical Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, Iran; [g]Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden

Keywords
Selective immunoglobulin A deficiency · Primary immunodeficiency · B cells defect · T cells defect · Genetic defect · Cytokine defect

Abstract
Selective immunoglobulin A deficiency (SIgAD) is the most prevalent type of primary immunodeficiency disorder. The phenotypic feature of SIgAD is related to a defect in B lymphocyte differentiation into plasma cell-producing immunoglobulin A (IgA). In this review, we summarize the recent advances in this regard. Genetic (including major histocompatibility complex [MHC] and non-MHC genes), immunologic (including B and T lymphocyte subsets abnormality), cytokines/chemokines and their related receptors, apoptosis and microbiota defects are reviewed. The mechanisms leading to SIgAD are most likely multifactorial and it can be speculated that several pathways controlling B cells functions or regulating epigenetic of the *IGHA* gene encoding constant region of IgA heavy chain and long-term survival of IgA switched memory B cells and plasma cells may be defective in different SIgAD patients.

Introduction

Immunoglobulin A (IgA) is the second dominant isotype in the blood circulation following IgG. In humans, there are 2 subclasses of IgA: IgA1 (main IgA subclass) and IgA2 (secreting in large bowel and least in the jejunum). IgA can be found in both monomeric and dimeric forms; circulating IgA is in monomeric form, whereas secretory IgA, in the mucosal secretions of respiratory, intestinal, and genitourinary systems, is dimeric. The monomeric structure of serum IgA has 2 heavy chains, each

Edited by: H.-U. Simon, Bern.

E-Mail karger@karger.com
www.karger.com/iaa

Prof. Asghar Aghamohammadi
Children's Medical Center Hospital
62 Qarib Street, Keshavarz Blvd.
Tehran 14194 (Iran)
E-Mail aghamohammadi@sina.tums.ac.ir

consisting of one variable and 3 constant regions, and 2 light chains, each of which is made up of one variable and one constant region [1].

Predominantly antibody deficiencies are the most frequent type of primary immunodeficiency disorders (PIDs), with more than 13,000 symptomatic patients registered globally (~20% of all reported PID patients to date) [2]. Selective immunoglobulin A deficiency (SIgAD), the most prevalent of PID, is characterized by decreased serum IgA level lower than 7 mg/dL in individuals older than 4 years with normal levels of IgM and IgG in serum and exclusion of other causes of hypogammaglobulinemia. These patients have normal IgG antibody response to all vaccinations but might be associated with a non-prominent T cell defect [3]. The prevalence varies due to the different ethnics, such as 1:142 in the Arabian Peninsula [4], 1:300–1:700 in Iran [5], 1:600 in the Caucasian population [6], and 1:18,500 in Japan [7]. The prevalence of SIgAD in Chinese population is higher compared to Japanese populations, 1:4,100 among 6 nationalities in China [8] and 1:1,615 in Chinese blood donors [9].

IgA deficiency demonstrates heterogeneous phenotypes – ranging from being benign, with asymptomatic individuals and diagnosed coincidentally through blood donor screening, to being problematic and symptomatic with different clinical manifestations including mild recurrent sinopulmonary infection, autoimmunity, allergy and occasionally with severe immunologic complications [10]. Based on the several efforts to clarify the etiology and pathogenesis of SIgAD, the major problem is the failure of B lymphocyte to produce IgA [11, 12]. However, other abnormalities such as increased lymphocytic apoptosis, cytokine network, signaling pathway by costimulatory molecules and also the presence of predisposing major histocompatibility complex (MHC) alleles might be involved in the pathogenesis of SIgAD [13–15].

Bringing this condition to a broader audience can help enlighten the enigmatic etiology and pathogenesis of SIgAD as a vital step for better understanding of the disease mechanism and better management of affected individuals. In this review, we summarize the recent advances in the field of SIgAD.

Pathogenesis of SIgAD

Recent findings have proposed that patients with SIgAD have defects in the process of IgA class switch recombination (CSR), production, and secretion of IgA as well as long-term survival of IgA switched memory B cells and plasma cells. These 4 main steps in the generation and maintenance of serum IgA level may be affected by genetic susceptibility elements, cytokines and their receptors milieu and gut microbiota, that are explained in next sections (Fig. 1).

Genetic Susceptibility

From a genetic point of view, 3 chromosomes including 18, 14, and 6 have been significantly associated with IgA deficiency according to the genome-wide association studies [16]. In this sense, the mode of inheritance is not fully understood; certain human leukocyte antigens (HLA) haplotypes and non-HLA genes have been associated with IgA deficiency. Modifying genetic factors and genetic associations, which may contribute either to the pathogenesis of the IgAD or other visible complications among patients, were suggested by studies that evaluated the underlying genetic defects of patients. In reported familial cases, inheritance of IgA deficiency is either autosomal dominant or autosomal recessive based on the pedigree analysis, but sporadic cases show no genetic associations [16, 17]. To date, identified defects of both MHC and non-MHC genes are summarized in the following sections.

MHC Genes

Since 1970, there are ongoing researches towards finding associations of HLA and IgAD predisposition which identified different loci of MHC regions [18–22]. Common genetic associations of the happenstance manifestations like autoimmunity, inflammatory complications, and malignancies in IgA-deficient individuals has helped to explore predisposing alleles of SIgAD [3, 23–25] (Table 1).

Except the geographical clustering of the association between HLA haplotypes and SIgAD occurrence, collectively, HLA A1, B8, B12, B13, B14, B40, DR1, DR2, DR3, DR7, DR11, DQ2, DQ3, and DQ5 alleles have been associated with SIgAD, either in a protective or predisposing pattern [22, 26–30]. Up to now, homozygosity and heterozygosity for the HLA-B8-DR3-DQ2, HLA-DR7-DQ2, and HLA-B14-DR1-DQ5 haplotypes have constituted strong risk factors for the development of SIgAD, while HLA-DR15-DQ6 has protected against SIgAD [21, 29, 31, 32]. Due to the linkage disequilibrium across MHC alleles, haplotypes containing aforementioned alleles can be related to other genes; thus, it is highly recommended to study single HLA genes, specific heterodimers, and complex interactions between alleles at multiple genes in MHC region.

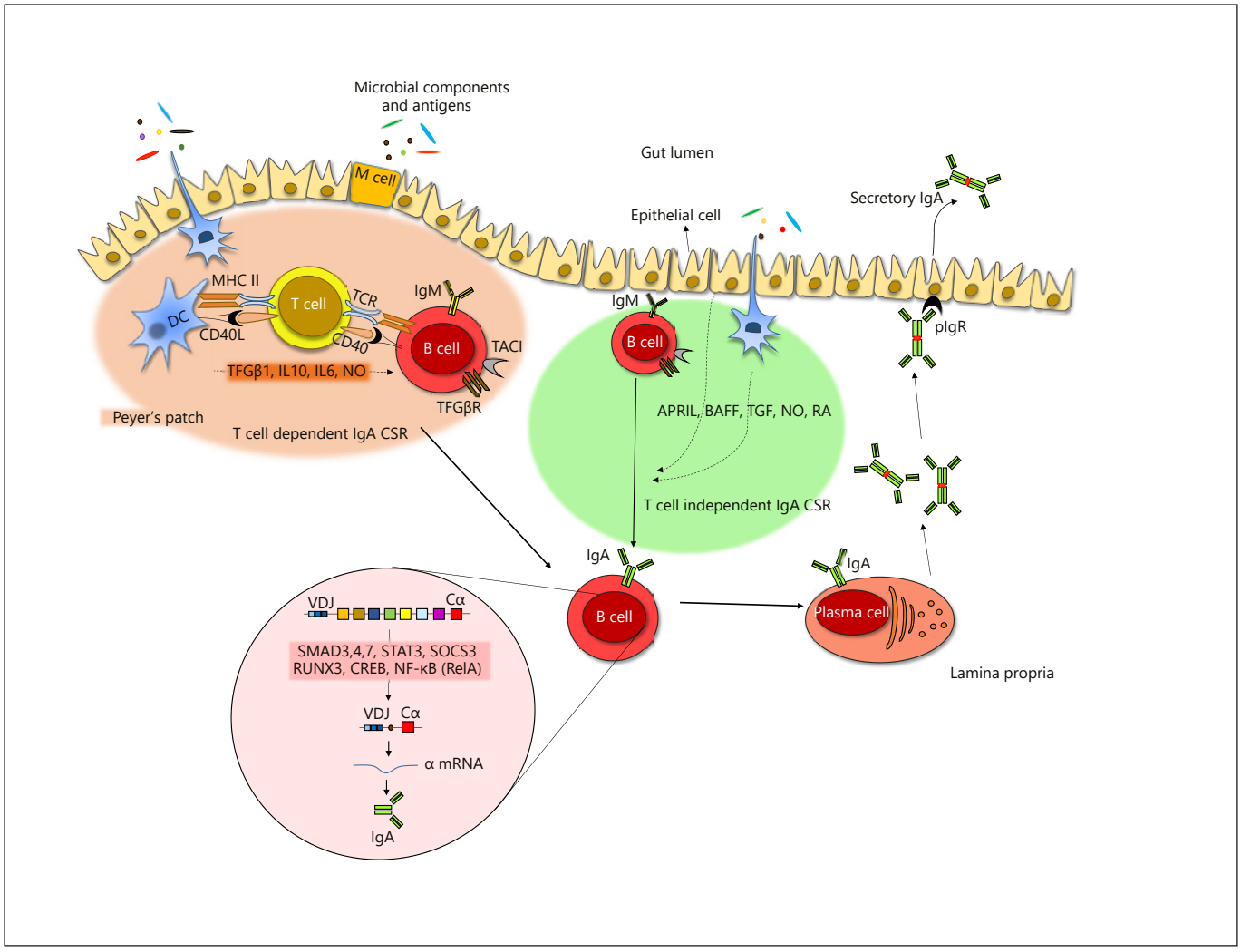

Fig. 1. IgA class switching in the gut. There are two pathways of IgA CSR to the dependency on T cells. TD pathway happens in germinal center and needs B and $CD4^+$ T cell interaction through CD40-CD40L and TGF-β1 production (Orange circle). TID IgA CSR occurs by engagement of different receptors, transcription factors, and cytokines such as nitric oxide, retinoic acid, IL-6, TACI, BAFF, APRIL, and TSLP in lamina propria (Green circle). TGF-β1 plays its role via SMADs, RUNX3 to induce IgA CSR. DCs by antigen capturing and presenting or secretion of cytokines are important in both 2 pathways. After class switching, DCs and epithelial cells via APRIL, BAFF and IL-10 induce plasma-cell differentiation. MHC, major histocompatibility complex; IgA, immunoglobulin A; TACI, transmembrane activator and CAML interactor; TGF-β, transforming growth factor beta; CSR, class switch recombination; NO, nitric oxide; RA, retinoic acid; TID, T-cell-independent.

The contribution of the HLA class II genes in susceptibility to SIgAD is determined in the context of HLA-DQB1*02:01, HLA-DQB1*0202, HLA-DRB1*01:02, HLA-DRB1*0301, and HLA-DRB1*0701 [33], while the highly protective association is reported for HLA-DRB1*15:01 allele. Moreover, a negative association between HLA-DR2-DQB1*0602 alleles were indicated. Risk alleles located between BTNL2 and HLA-DRA regions are in linkage disequilibrium with HLA-DRB1*15:01 and suggested to play a protective role in SIgAD too [30, 33].

Other allelic mutations among included genes in MHC region are also reported in patients with SIgAD such as *MSH5*, which itself showed contrast association with HLA-B14-DR1 and HLA-B8-DR3 haplotypes, and *IGAD1* which has a locus within HLA-DQ/DR located at the telomeric part of the class II region or the centromeric part of the class III region of the MHC [27, 34, 35]. There are also some complement encoding genes that have been suggested to be connected with the pathogenesis of IgAD, most of them (including C4A, C4B, and C2) being located in the

Table 1. Proposed genetic etiologies underlying IgA deficiency

Name	Function		Immune disorders with common predisposing locus	Reference
MHC genes				
MHC I region (A1, B8, B12, B13, B14, B40, C7)	*Protective* Susceptibility	HLA-A*0101 HLA-Cw*0701 HLA-B*0801 HLA-B*1402	Celiac disease, Myasthenia gravis, Rheumatoid arthritis	[18–22, 27–30, 33, 34]
MHC II region (DR1, DR2, DR3, DR7, DR15, DQ2, DQ5, and DQ6)	Protective	HLA-DRB1*15 HLA-DQB1*0301 HLA-DQB1*06	Autoimmunity (SLE, graves, T1D, Celiac disease, Myasthenia gravis, Rheumatoid arthritis)	
	Susceptibility	HLA-DQB1*02 HLA-DQB1*05 HLA-DQA1*0501 HLA-DRB1*0102 HLA-DRB1*0301 HLA-DRB1*0701 HLA-DRB1*0102		
MHC III region	Encoding complement genes (C4A, C4B, and C2) and mismatch repair proteins			[34, 35, 115]
DQ3 *MSH5* *IGAD1*	Predisposing locus on the HLA DR1 and DR7 haplotypes			
Non-MHC genes				
JAK3	T cell receptor signaling		Combined immunodeficiency	[116–120]
DOCK8	Controlling both actins cytoskeleton-dependent and – independent immune responses			
LRBA, *CD27,CD70*	Costimulatory mechanisms			
DCLRE1C, *RAG1*	DNA repair systems			
WAS, ATM, PNP, TTC7	Thymic functions		Syndromic combined immunodeficiency	[121–128]
CHD7, *DKC1*, *RMRP, DNMT3B, MECP2, TINF2, PL24*	Epigenetic markers			
NBS1, PMS2, RNF168, RAD50, MLH1	DNA repair process			
BTK, *TACI, PRKDC*	B cell activation and development		Antibody deficiency disorders	[123, 129–136]
VAV1, PI3KCD, *PLCG2, PIK3R1, TNFRSF13B*	Signaling			
IKZF1	Immune cell development			
MSH2, MSH6, NFKB1, NFKB2	NF-kB activation pathway			
TWEAK, *CARD11*	Apoptosis			
CYBB, *RAC2, NCF1, SBDS*	Motility and respiratory burst of phagocytes		Phagocyte defectiveness	[137–142]
XIAP	Coding an X-linked inhibitor of apoptosis protein		Dysregulated immunity and signaling pathway, and autoimmune disorders	[143]
IFIH1	Encodes MDA5 (a cytosolic receptor that recognizes dsRNA and initiates interferon pathway activation)			[144, 145]
CXCR4	A CXC chemokine receptor gene			[146, 147]

Table 1. (continued)

Name	Function	Immune disorders with common predisposing locus	Reference
STAT1, *STAT2, STAT3, IL12RB1*, and *C3*	Inducer of involved factors of cell viability in response to stimuli and pathogen	Intrinsic and innate immunity	[148–150]
NLRP12, and MVK		Auto inflammatory disorders genes affecting the inflammasome	
Polymorphism			
CLEC16A	Negatively regulates autophagy via modulation of mTOR activity	Autoimmune diseases including MS, T1D, SLE, and Celiac disease	[38, 145, 151, 152]
AICDA	Somatic hyper mutation, gene conversion, and class-switch recombination of immunoglobulin genes	Hyper-immunoglobulin M syndrome	
CDH23	Encoding the calcium-dependent cell-cell adhesion glycoproteins	Non-syndromic autosomal recessive deafness, upregulated in breast cancer	
TM7SF3	Maintenance of protein homeostasis and promoting cell survival through attenuation of ER stress		
CTLA4, ICOS, FAS	Immune checkpoint protein	Graves' disease	
TNFAIP3	Inhibition of NF-kB activation	Autoimmune diseases including SLE	
IL-10	Anti-inflammatory cytokine		
IL6	Stimulation of acute phase responses, hematopoiesis, and immune reactions		
PVT1	Oncogenic long noncoding RNAs	RA	

HLA III region. The presence of proper MHC molecules play an important role in presenting antigen from B cell to T follicular helper (TFH) cell and the consequent cytokine production. This helps in ensuring optimum establishment of long lasting IgA switched memory B cell and plasma cell. Altogether, the complex and multi-locus MHC associations leading to predisposition/protection of IgAD needs to be clarified to shed light on the exact underlying pathogenesis of SIgAD. Interestingly, consistent with previous analytical studies of HLA, it has been manifested that unusual HLA markers in SIgAD patients predict the possibility of progression to common variable immunodeficiency disease (CVID) [28, 29, 36].

Non-MHC Genes

It has been manifested that MHC locus performs the most important role in both immunologic response and tolerance; however, non-MHC genes are also considered as a cause of many immunological deficiencies. To address the potential genes arising from selective IgA deficiency, we summarized the non-MHC genetic defects of individuals who had reduced IgA levels as a common clinical manifestation. Among the involved molecules in the T cell receptor signaling, costimulatory mechanisms, and DNA repair systems, gene defects have been reported. In this category, *JAK3* and *RAG1* genes and some of the other mutated genes are illustrated in Table 1. Thymic functions and epigenetic markers are also reported to be defective through mutated genes; like *ATM* gene, a coding element of an involved protein in the nervous and immune system. It has also been demonstrated that some responsible genes in the B cell receptor (BCR) signaling, like *BTK* and *transmembrane activator and CAML interactor*, are modifying factors in a number of IgAD individuals. There are some other reported non-MHC gene mutations in immune disorders who had IgAD (Table 1) [15, 37]. Non-MHC loci polymorphism of some genes listed in Table 1 have been reported to be associated with SIgAD [38].

From the discovery time of IgAD, Ig heavy-chain constant region (C) gene alpha (IGHA) and Iα germline transcript (α-GLT) were the most suspected responsible elements for SIgAD. In 1984, Migone et al. [39] showed large DNA deletion in the constant region of Ig heavy chain in 2 patients with reduced serum Igs. In 1991, more single and multigene deletions were found in the Ig CH locus of 15 Tunisian individuals who lacked several immunoglobulins [39, 40].

During an investigation about the molecular events leading to IgA production in IgAD patients, in 1994, Islam et al. [41] indicated a significant decrease in the number of switch (S) mu/S alpha fragments in unstimulated peripheral blood mononuclear cell (PBMC) of IgAD patients. The membrane mRNA expression of C alpha in unstimulated PBMC decreased along with C alpha mRNA levels and IgA production in PWM-stimulated PBMC. Therefore, a failure to switch to IgA-producing B lymphocytes or a compromised survival of such cells were suggested to be causal in IgA deficiency [41]. Moreover, in 1999, Wang et al. [42] found a low expression of both secreted and membrane forms of productive C alpha mRNA in IgA-switched B cells and impaired IgA switching. Therefore, a direct link to low IgA secretion and a blockade in post-IgA switch differentiation of B cells was suggested in IgA-deficient subjects who were homozygous for HLA-B8, SC01, DR3 haplotype [42]. However, Asano et al. [43] found reduced α-GLT expression and absence of α circle transcripts in SIgAD in contrast to partial IgAD patients; they studied a group consisting of 3 SIgAD and 3 partial IgAD patients to clarify the probable stage in which B cell differentiation may be blocked. Among SIgAD patients, they observed normal induction of α-GLT and α circle transcript after stimulations with phorbol myristate acetate and transforming growth factor beta (TGF-β) as well as IgA secretion via stimulation with anti-CD40, IL-4, and IL-10. These observations were different in partial IgAD patients. Consequently, they established the importance of decreased expression level of α-GLT in the pathogenesis of SIgAD [43]. In 2006, however, Hummelshoj et al. [44] showed a reduced GLT-α and activation-induced cytidine deaminase (AID) expression upon stimulation of naïve IgD^+ B cells with TGF-β, IFN-γ, and IL-10 in IgAD individuals and proposed that a low α-GLT underlies low level of productive IgA and further differentiation into plasma cells. In 2009, a combination of IL-21, IL-4, and anti-CD40 stimulation induced CSR (α- and γ-GLT) to IgG and IgA and differentiation of Ig-secreting cells in CVID or IgAD patients [45].

Taken together, a much debated question exists whether a defect in the *IGHA* gene and associated genetic disorder causes IgA deficiency or epigenetic modifications and non-genetic events. Recent investigations have suggested post-switch defects hypothesis, including intrinsic transcriptional defects in B cells or a lack of proper activating signals for the *IGHA* gene that we have discussed in next sections. Furthermore, according to a recent interesting study, an intron-encoded microRNA (called miR-6891-5p) by HLA-B locus has been described for its functional role in modulating the expression of *IGHA1* and *IGHA2* [46], which presents a post-transcriptional hurdle in the IgA production process.

Except for the predefined paradigm of cytogenetic abnormalities (e.g., 4p monosomy, trisomy 8, trisomy 10p, translocation of 10q to 4p, 17p11.2 deletions, 18q-syndrome, trisomy 21, monosomy 22, and 22q11.2 deletion syndrome) [15] and HLA haplotypes association for SIgAD pathogenesis, monogenic mutations should be considered as a separate etiology [13]. The strategy to classify IgA-deficient patients in homogenized groups will be helpful in SIgAD pathogenesis, besides taking an imbalanced genetic approach using high-throughput sequencing.

Immunologic Defects

Correct immunological interactions originate from an intact genetic content. A phenotypic immunological feature might reflect the underlying genetic background defects in SIgAD patients. In this line, several immunologic perturbations can account for an impaired B-cell maturation, plasma cell differentiation, and long-term IgA production in SIgAD patients. These immunologic dysregulations have been observed from abnormal bone marrow progenitors and mature B cells profile to inadequate expression of costimulatory molecules or production of cytokines at local sites of B-cell proliferation, including primary and secondary lymphoid tissues. Therefore, one of the most important causes of SIgAD is related to numerical and functional defect in B lymphocytes and other immune system components [13].

Hematopoietic Stem Cells

Stem cells are the undifferentiated class of cells that have a potential to differentiate into different cell types such as immune precursors. In 1985, Hammarström et al. [47] showed that IgA deficiency can be transferred to recipients by bone marrow transplantation from an IgA-deficient donor. On the contrary, in 1991, Kurobane et al. [48] showed that bone marrow transplantation from a

normal individual could correct the impairment of IgA production. These 2 studies suggest the possibility of defects in stem cells of IgA-deficient patients. However, to develop a full picture of bone marrow transplantations' efficacy in IgA-deficient patients, additional studies will be needed as side effects may arise, as experienced in patients with CVID [49].

B Cell Subsets

Few studies have evaluated the measurement of B-lymphocyte subsets in SIgAD patients [11, 12, 50–52]. Litzman et al. [52] reported that there was no significant abnormality in the B-cell subsets of IgAD patients. However, further studies indicated decreased class-switched memory B cells in SIgAD patients [11, 12]. In this line, we indicated in one study that there are 2 subgroups of patients with IgAD (group I and II) based on switched memory B cells percentage [50]. In patients with group I, the percentage of switched memory B cells are less than 0.4%, while in patients with group II the percentage of switched memory B cells are more than 0.4%. Based on this categorization, we found that patients with low-switched memory B cells exhibited more severe clinical features, including pneumonia, bronchiectasis, and autoimmune diseases than group II [50]. The classification of SIgAD patients by assessment of switched memory B cells could help physicians with the clinical prognosis for these patients.

Nechvatalova et al. [11] evaluated similarities between CVID and IgAD based on the determination of B-lymphocyte subsets. They indicated a decrease in the frequency of switched memory cells, transitional cells as well as plasmablasts, and an increase in the $CD21^{low}$ B cell subset compared to healthy individuals [53, 11]. In this sense, Celiksoy et al. [51] demonstrated high counts of naive B cells in patients with SIgAD similar to CVID patients. On the contrary, it has been evident that increase of naïve B cells have an association with autoimmunity occurrence and it can similarly be observed in the autoimmune patients with IgA deficiency and other forms of antibody deficiency (e.g., selective IgM deficiency, and CVID) [51, 54]. Since there is evidence about the progression of SIgAD towards CVID, the immunologic profile association of these 2 antibody deficiency is logical [55].

T Cell Subsets

Antibody isotype switching and production can be influenced by different subpopulations of T cells and are also important in the B cell maturation in the germinal center. However, in some studies, investigators have demonstrated no significant difference between SIgAD patients and healthy controls for any of the measured T-cell subpopulations ($CD3^+$, $CD4^+$, $CD8^+$, naïve, memory, and differentiated T cells) and the proliferation index and the percentage of divided cells [11, 12]. Moreover, Lemarquis et al. [12] assessed effector T cell subpopulation functions and have shown that the activity of TH1, TH2, TH17, TH22, and T TFH cell are comparable in SIgAD patients compared to healthy controls. Only one study by our group has reflected a defect in regulatory T cells (Tregs) in SIgAD patients with autoimmunity [56]. The recent group also reported comparable function for natural Tregs (nTregs) and induced Tregs (iTregs) between SIgAD patients and healthy controls. Similarly, the diagnostic criteria suggested by the European society for immunodeficiency include the exclusion of T cell defects in the SIgAD patients (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria).

Receptor Defects

It has been recently demonstrated that a defect in different immune receptors could be involved in the pathogenesis of SIgAD. T-cell-dependent (TD) pathway drive B cells in germinal center after interaction with TFH through CD40 ligand (CD40L)-CD40 and TGF-β1 production (Fig. 1). TGF-β1 has an important role in the induction of IgA CSR via different transcription factors such as SMAD, Runt-related transcription factor 3 (Runx3), and PU1. This happens through the involvement of CD40L on the $CD4^+$ T cells to induce nuclear factor kappa light chain enhancer of activated B cells (NF-κB) activation, which activates activation-induced cytidine deaminase expression as a crucial requirement of CSR. T-cell-independent (TID) IgA CSR occurs by engagement of different receptors, transcription factors, and cytokines such as toll-like receptor, B BCR, nitric oxide (NO), retinoic acid (RA), IL-6, TACI, BAFF, A proliferation-inducing ligand (APRIL), and thymic stromal lymphopoietin. There are, however, other possible theories such as the theory of antibody against cytokine and cytokine receptors. Therefore, defective receptors or disturbed signaling pathways of each of these factors might be involved in IgA-deficient patients [57–59].

IgA Expression as a BCR

B cells use their antigen receptor to capture small amounts of their specific target and to present peptide antigens to T cells; so, low levels of surface IgA expression may lead to low capacity of those B cells to present anti-

gens, and therefore they do not receive adequate co-stimulation for their terminal differentiation. The surface expression of IgA is necessary for IgA secretion process. It has been indicated that the expression of the membrane and secreted *IGHA* gene decreased, and it may be one of the post class switch defects causing IgA deficiency [42]. Nevertheless, Schaffer et al. [60] reported normal percentages of IgA B cells and normal levels of surface IgA expression in some IgA-deficient patients, suggesting a defect in secretion of IgA but not IgA expression. These results cannot exactly explain the IgA expression's defect in SIgAD patients and further studies with more focus on the surface expression of IgA on B lymphocyte are therefore suggested.

TGF-β Receptor

The IgA CSR and secretion can be induced via TGF-β dependent and independent mechanisms. Using mouse model that selectively lack TGF β receptor on B cells, some studies have reported a defect in IgA production, especially in mice with defect in TGF-β receptor II than in those with deficient TGF-β receptor I [61, 62]. Although decreased IgA secretion in TGF-β receptor deficient mouse model demonstrated the possible role of this pathway in human SIgAD, to clarify a full picture of the role of TGF-β receptor in the pathogenesis of SIgAD, additional studies are required. SMAD proteins act as transcriptional factors and transducers in the TGF-β1 signaling pathway. A strong relationship has been reported between SMAD3, SMAD4, and SMAD7, and regulation of IgA-CSR [59]. In this line, overexpression of SMAD3 and SMAD4 selectively increase IgA production and surface expression, besides, SMAD3 deficient mice model found with no IgA. On the contrary, SMAD7 (as an inhibitor of TGF-β receptor signaling) deficient mice model have increased CSR towards IgA, so over activity of this checkpoint inhibitors can also decrease the IgA production. It has also been shown that SMAD7 abolishes the synergistic effect of SMAD3 and SMAD4 on *IGHA* promoter activity [63–65]. Moreover, acute myeloid leukemia and CAMP-response element-binding protein transcription factors have been shown to collaborate with SMADs to activate the transcription of α-GLT in response to TGF-β [66]. In addition to these factors, lymphocytes of mice with Rel-A (NF-kB subunit also known as p65) deficiency present a selective defect in the secretion of IgG1 and IgA, which suggests a candidate for future studies [67]. Therefore, defect in TGF-β receptors and down stream's transcription factors can have an important role in SIgAD. Despite these promising findings, the role of defects in these transcription factors in human SIgAD remains unclear and further studies, which take these variables into account in a human study, will need to be undertaken.

IL-10 Receptor

Differences in cytokines and their receptors exist within IgA-deficient patients. Several researches have focused on the phenotypic heterogeneity in IgA-deficient patients. They have found that under suitable stimulations, B cells of healthy IgA-deficient individuals synthesize considerable amounts of IgA [68]. But B cells from infection-prone IgA-deficient patients produce only minute levels of IgA. So these data suggest that the abnormalities of B cell differentiation in IgA deficiency can be compensated by cytokine stimulation but they react heterogeneously [69, 44]. Another important finding by further investigations were that stimulation of IL-10/IL-10 receptor is not sufficient to induce IgA production and interestingly with additional IL-4 in the culture media a higher amount of IgA can be produced [44, 70]. Similar to these observations, in 1998, it has been shown that IL-10 stimulation leads to increased IgA in IgA-deficient subjects, but not in IgA level production of healthy controls. The synergizing effect of IL-4 and IL-10 on IgA production in IgA-deficient group, specifically to IgA isotype, has also been asserted [70]. Borte et al. [45], however, reported a higher efficiency of stimulation with IL-21 compared to stimulation with IL-10 or IL-4, because IL-21 is one of the important promoters of human B cells differentiation into plasma cells. Nevertheless, *IL21* gene sequencing did not reveal any mutations and there were no defects in the analysis of IL-21 receptor and IL-21 mRNA expression in SIgAD patients, so IL21 can be a potential therapeutic agent to reconstitute antibody production in SIgAD patients [45]. This result has raised a question whether a probable defect in IL-10/IL-10 receptor response exists in these patients. Interestingly it was shown that in contrast to IL-10 other members of the interleukin-10 subfamily (IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29) failed to induce the production of any immunoglobulin by stimulation of purified naive B cells [71]. It should be noted that no defects were observed in IL-10 production in SIgAD patients [72]. Despite many unanswered questions about molecular mechanisms of an IL-10 signaling pathway, it can be hypothesized that lack of TGF-β receptors up-regulation cause IgA deficiency and IL-10 may be a prerequisite for TGF-β II receptor expression and subsequent deliverance of the class switch signal. These rela-

tionships may be partly explained by the finding that IL-10/IL-10 receptor interaction has the capability to enhance TGF-β receptor II expression on activated T cells [73].

BAFF and APRIL Receptors

Another possible reason for the production of defective IgA can be a defect in related co-stimulatory BCRs and their signaling pathways. As noted, BAFF (B-cell activating factor) and APRIL are 2 important cytokines in TID IgA CSR. B cells express 3 receptors for these cytokines, including TACI, BAFF receptor (BAFF-R), and B-cell maturation antigen. APRIL interacts with TACI and B-cell maturation antigen but BAFF can bind to all 3 receptors [74]. BAFF is a positive regulator of B cells which enhances B-cell survival, and with low probability, its defect cannot lead to just IgA deficiency, because BAFF-R and BAFF knockout (KO) mice are deficient in B cells and they cannot be used to investigate the requirements of IgA induction [75]. Although it reported two siblings with CVID that carry a homozygous deletion in the BAFF-R gene, have lower IgM and IgG serum levels but, unlike most CVID patients, they have normal IgA concentrations [76].

TACI or TNFRSF13B (tumor necrosis factor receptor superfamily member 13B), encoded by the *TNFRSF13B* gene, is a transmembrane protein of the TNF receptor superfamily. TACI has an important role in antibody responses against different types of antigens. Several polymorphic mutations have been found in the *TNFRSF13B* gene in IgA-deficient individuals, which is discussed in the genetic defects section. It has been manifested that TACI-KO mice have low immunoglobulin levels, particularly IgA and present weak immune responses to TID antigens [77, 78]. Findings from several animal studies have indicated inappropriate levels of TACI signaling in the disruption of the immune system and promotion of autoimmune disorders [79]. Furthermore, in 2005, Castigli et al. [80] showed that in vitro stimulation of murine B cells using APRIL via TACI activation leads to IgA, IgG and IgE CSR, while TACI-deficient B cells were not able to switch to IgA when stimulated by BAFF in spite of their capability to switch to IgG and IgE. Thus, it seems that interactions of APRIL-TACI is necessary for IgA production [59, 80]. This is in contrary to the findings by Bacchelli et al. [81] that suggested an insignificant role of TACI in IgA CSR in vivo despite the previously observed evidence in vitro. So, further progress in determining the correct role of these factors in SIgAD patients is required.

CD40L Receptor

T lymphocyte cells are important in IgA CSR via CD40/CD40L interaction, which is expressed on activated TFH and provides the second signal for TD CSR. Therefore, defective immunoglobulin production has been speculated to be due to an impaired or decreased helper T-cell activity in some SIgAD patients [52]. Cassidy et al. [82] compared the ability of SIgAD patients' T cells to help antibody production via normal B cells, surprisingly, no differences were found in the production of IgM, IgG, and IgA, either in the presence of normal or patients' T cells. T cells of SIgAD patients did not suppress IgA production and surprisingly helped the production of IgA [82, 83]. On the contrary, there are several evidences that have shown the correct IgA production when a deficiency exists in CD40 or CD40L in humans and mice, for instance, in experimental murine with rotavirus infection, virus clearance was achieved via induction of specific IgA, even in T-cell deficient animals [59, 84, 85]. Although some studies have proposed a possible CD40L deficiency in SIgAD patients, B cells of patients showed a reduced proliferative response to CD40L [86], and further support the idea that the probability of T-cell deficiency in SIgAD patients is low.

Chemokine Receptors

Aside from accuracy of stimulators in IgA production machinery, B cell homing to peripheral and mucosal tissues have an important role for IgA production and secretion for long-term memory B cell generation and homing/survival of plasma cells within the bone marrow. B cell homing is mediated by specific adhesion molecules and chemokine receptors such as CCR9, CXCR4, and CCR10 that are important for homing to the small intestine and bone marrow by CCL25 ligand and CCL28 ligand, respectively [87]. A recent study showed that the proportion of the mucosal CXCR4, CCR10, and α4β7 homing receptors expression are comparable in SIgAD individuals and healthy controls [12]. Although some studies have shown that expression of homing receptors are normal in SIgAD patients but more broadly, research is also needed to prove these results.

Cytokine Network Defects

A balanced and tuned cytokine profile are other important elements of signaling that are generally required for CSR. They activate transcription of promoters located in the upstream of CH exons and former switch region [59, 88]. This cytokine profile may be changed due to the abnormality of B-, T-, and dendritic cells (DC) interac-

tions since the generation of signals for B cell differentiation into IgA-producing cells requires this network. As mentioned earlier in cytokine receptors' section, there are several cytokines that induce IgA CSR and terminal differentiation of stimulated B lymphocyte. The major cytokine for IgA CSR is TGF-β which works with the contribution of other interleukins, such as IL-2, IL-4, IL-5, IL-6, and IL-10 [58, 59]. The ability of SIgAD patient's PBMCs for producing several cytokines was analyzed; however only an increased production of TNF has been observed, suggesting that TNF may be involved in the regulation of IgA production [89]. In 1995, Müller et al. [90] have reported reduced serum levels of TGF-β in SIgAD patients. However, some studies reported no difference in the plasma level of TGF-β1 and TGF-β1 mRNA expression of B cells between SIgAD patients and controls [43, 45, 90]. Although TGF-β1 dysregulation might be a contributing factor in the pathogenesis of SIgAD, it should be noted that B cells generally undergo the CSR in the secondary lymphoid organs and it would be more valuable to analyze TGF-β1 expression in germinal centers.

DCs of the Peyer's patches and other mucosal associated lymphoid organs are involved in IgA CSR via several cellular interactions. DCs activate latent form of TGF-β1 by induction of the processing of a latency associated peptide, presenting bacterial products to B cells and secreting necessary cytokines for IgA CSR, such as TGF-β, IL-10, BAFF, and APRIL (Fig. 1) [91]. Among different types of DCs, intestinal DCs constitutively secrete RA in both humans and mice. RA has an important role in both TD and TID IgA CSR [87, 92]. In addition, RA is involved in plasma cell differentiation and CCR9 expression that are essential for homing of naive B cells to the small intestine [93, 94]. Runx3 plays a key role in IgA CSR as an acting molecule downstream of RA and TGF-β1 signaling, and IgA production is blocked in Runx2-Runx3 double-deficient mice [93]. However, Park et al. [95] found RA to act through RA receptor pathway, where neither Runx3 nor SMAD3/4 is involved, and SIgAD may be caused by a defect in RA receptor signaling pathway. In addition, DCs have an important enzyme entitled nitric oxide synthase (NOS) that catalyze the production of NO from L-arginine. It has been reported that IgA CSR is impaired in inducible NOS KO deficient mice. Transferring wild-type DCs to inducible NOS KO mice rescued IgA production in these mice. On the contrary, it has been indicated that the Runx3 (as a RA downstream molecule) is significantly low in iNOS-deficient B cells [96]. Thus, due to the important role of DCs in CSR process, defects in RA and iNOS signaling may be involved in the pathogenesis of SIgAD; however, further studies on abovementioned molecules and factors are needed in humans.

BAFF and APRIL are 2 important cytokines in TID IgA CSR. BAFF KO mice showed a slight decrease in mucosal and serum IgA levels. However, APRIL KO mice had normal serum IgA levels and mucosal IgA levels comparable to wild-type mice; however, IgA producing plasma cells in the lamina propria were reduced in APRIL-deficient mice [97, 98]. On the contrary, APRIL and BAFF plasma levels of SIgAD and CVID patients were significantly higher than those of healthy children. These findings indicate that APRIL and BAFF may be involved in the pathogenesis of SIgAD [99].

Peyer's patch organogenesis requires several factors like lymphotoxin (LT). It should be noted that although LT-α, LT-β, and LT-β receptor deficient mice have a lack of lymph nodes and Peyer's patches, and do not produce intestinal IgA [100, 101], but whether IgA production in the reticuloendothelial organs like bone marrow would also be affected remains to be investigated.

Despite isolated defects in several cytokines including IL-4, IL-6, IL-7, and IL-10, which have been found in SIgAD patients [13], it should be noted that synergistic action between cytokines occurs in the secondary lymphoid organs and leads to robust IgA production. Therefore, combined abnormal cytokine releasing pattern at local sites of B-cell proliferation or cytokine kinetics can also account for the failure of IgA production in SIgAD patients. Alternatively, some cytokines may act as inhibitory factors of B lymphocyte function. Further studies, which take these variables into account, will need to be undertaken.

Apoptosis

Increased apoptosis of B cells during an immune response can be involved in the reduction of IgA secretion and differentiation into plasma cells or long-term IgA switched memory B cells and plasma cells. Initial investigations studied the cellular and molecular mechanisms underlying IgA deficiency, and reported that IgA-positive B-lymphocytes can be found in patients with IgA deficiency [102]. Decreased number of $CD138^{+}XBP1^{+}$ plasma cells was observed upon stimulation with TGF-β and IL-10, but when the same stimulation was used in combination with IL-4, B cells were able to induce transcription of intracellular XBP-1, indicating that the defect is not due to the inability of B cells to differentiate into plasma cells. These results seem to be consistent with reports showing increased apoptosis of $CD20^{+}IgA^{+}$ B cells as a part of casual etiology of SIgAD [43, 103]. In this regard, Hammarström

and colleagues [45] reported that SIgAD patients lack surface IgA B cells, and the combination of IL-4, IL-21, and the anti-CD40 monoclonal antibody can prevent apoptosis of these cells in SIgAD patients, and result in reconstitution of IgA secretion. A notable point is that in spite of the intact genes and molecular mechanisms of IgA recombination, and in addition to the reports that show low surface IgA-positive B cells in patients with SIgAD, the existence of a defect in the long-term survival of IgA secreting cells and memory B cells should be considered [14].

Microbiota Defect

Production of IgA in the intestinal mucosa depends on colonization with environmental microbes; however, Bendalec and colleagues [104] showed that the interaction of the microbiome for IgA stimulation is not specific to particular bacterial epitopes, and produced IgA that can widely react with different components of the gut commensal microbes.

Hence, it can be hypothesized that defects in commensal intestinal microbes cause IgA deficiency. Interestingly, it has been manifested that despite strongly reduced IgA level observed in intestinal mucosa of germ-free mice, there was no IgA deficiency, and the serum IgA level was about half the normal quantity [105–107]. This suggests that because of separate circuits of mucosal and systemic IgA production, amount of serum IgA can be produced independently in mucosal layers. Although the gastrointestinal tract is the biggest mucosal surface area of the human body, other mucosal surfaces have a significant role in the final IgA production [108]. In general, however, commensal intestinal microbes are crucial for adjusting the level of induction of IgA synthesis. These SIgAD patients are expected to show more serious gastrointestinal problems if defects are present in microbiota. In addition to the necessity to study this concern, extensive research is needed to determine whether IgA production leads to defects in the bone marrow and spleen of SIgAD patients.

Animal Models for SIgAD

Animal models of human disease are commonly utilized to gain insight into the pathogenesis of diseases or to investigate the efficacy of potential therapeutic regimens and drugs. There are a number of reports on wolves, chickens and several breeds of dogs with IgA deficiency but the molecular basis of these deficiencies has not been discovered [109–112]. Since in mice, almost any given gene can be a manipulated, several suspected genes related to the IgA production have been switched off and examined for immunological and clinical consequences. Harriman et al. [113], for the first time, targeted the switch and constant regions of the *IGHA* gene in mice and produced IgA-deficient homozygous mice ($IgA^{-/-}$).

Subsequently, a member of the TNF superfamily were targeted and BAFF, APRILL, and TACI KO mice models have been generated [78, 80, 98]. Another notable model was wasted mouse, presenting a phenotype characteristic of ataxia telangiectasia, and Kaiserlian et al. [114] proposed these mice with concurrence of IgA deficiency. The most important issue is that even though these animal models are phenocopies of IgA deficiency in humans, none of them naturally happens and there is no animal model available yet which simulates the human IgA deficiency. Therefore, for better understanding of the pathogenesis of IgA deficiency and due to heterogeneous etiologies different animal models might be developed.

Conclusion

The purpose of the current review was to investigate the pathogenesis of SIgAD. We still need to increase our knowledge about the mechanisms and sites of alternative IgA CSR, as SIgAD can be associated with different PIDs. Despite these promising results, 1 question remains regarding the compensatory and complementary mechanisms for IgA CSR and production: why these patients generally do not have solely IgA. The mechanisms leading to SIgAD are most likely multifactorial rather than monogenetic and it can be speculated that several pathways controlling B cell functions or regulatory regions of the *IGHA* gene may be identified as underlying etiologies in different SIgAD patients. Thus, results of available animal models cannot be applied on humans with SIgAD, and for better understanding of the pathogenesis of IgA deficiency, different animal models need to be designed.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

None of the authors have any competing interests to declare.

Funding Sources

This work did not receive any specific grant.

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